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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/061,417	OLSON ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 17 August 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 5 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *17 June 2004*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☐ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *none*.

Claim(s) objected to: *none*.

Claim(s) rejected: *1, 4, 9*.

Claim(s) withdrawn from consideration: _____.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 1, 4, 9 are being examined.

The following are the remaining rejections.

MISCEALLANOUS

Applicant admission that the affidavits of Bush, Williams and Rosethermal submitted on July 09, 2003 were incorrectly filed and not relevant to the arguments herein is acknowledged.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Rejection under 35 USC 112, first paragraph of claims 1, 4, 9 pertaining to lack of a clear written description of small molecule inhibitors for use in the claimed method of treating hypertrophy, remains for reasons already of record in paper of 03/18/04.

Applicant argues that the examiner primarily cites to the Lilly case for the proposition that "an adequate written description of a DNA requires a precise definition" Applicants submit that examiner is attempting to create a rule of law from Lilly where none currently exists. Applicant argues that Lilly and its subsequent cases have not required that an invention must **always** be specifically described as Lilly required for those particular DNA molecules, nor do the cases require that a genus must be described in its entirely.

Applicant's argument is based on distorted interpretation of the Examiner's quotation of Lilly case, and thus is not found to be persuasive. The Examiner did not recite that Lilly requires that an invention must **always** be specifically described as Lilly required for those particular DNA molecules, nor that the case requires that a genus must be described in its entirely.

Rather the Examiner recited in the Office action of 07/17/01, on page 4, that "Although drawn specifically to the DNA art, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly relevant to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA..."requires a precise definition, such as by structure, formula, chemical name, or physical properties", not a mere wish or plan for obtaining the claimed chemical invention".

In the Office action of 03/18/04, the Examiner quotes Fiers, 984 F.2d at 1171, "The following teaching in the court clearly applies to the claimed invention. The court has held that statements in the specification describing the functional characteristics of a DNA molecule or methods of its isolation do not adequately describe a particular claimed DNA sequence. Instead "an adequate written description of DNA requires

more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1566-67 (quoting Fiers, 984 F.2d at 1171).

Applicant argues that the important point of both Lilly and Enzo cases is that function alone cannot support a set of claims to the molecules behind that function. Applicant argues that however, the present specification does not rely on function alone. Applicant argues that a number of the NF-AT3 targeting molecules disclosed by applicant are already known. Applicant argues that the specification goes beyond simply claiming an undescribed molecule, it actually refers to GATA4 mimetics, DTC's, antisense molecule (p27, lines 12-20), antibodies, competitive inhibitors of NF-AT3 (p.30, line 21), as well as other proteins that inhibit NF-AT3 (Summary on page 4, lines 15-25, and Examples 3, 6-9). Applicant argues that these examples describe specific molecules known in the art, whose mention alone should be sufficient to satisfy the written description requirement.

Applicant argues that the structure of GATA4 mimetics, and antisense molecules are defined by the prior art structures of the target molecules.

Applicant argues that Applicant is unaware that commonly structure is required for claiming a genus of inhibitors.

Applicant recites the Rochester case law. Applicant argues that current claims call out methods of treatment by inhibiting NF-AT3 and the specification then describes both in words and examples a variety of ways to accomplish the claimed method.

Applicant's arguments set forth in paper of 08/17/04 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that page 27, lines 12-20 in the specification of the instant application does not recite GATA4 mimetics, DTC's, antisense molecule. The specification does not recite DTC's, which was only recited in Applicant's response to the Office action. The specification contemplates the use of mimetics of beta-turns within GATA4, that binds to NF-AT3 in a manner analogous to the transcriptional factor GATA4, and specifically inhibits NF-AT3 binding to GATA4 (p.29, lines 13-25).

However, no disclosure of structure of any GATA4 mimetics is found in the specification.

Further, although the structure of NF-AT3 is known in the art, the structure of the particular small antisense molecules that inhibit **in vivo** function of NF-AT3 is not disclosed in the specification.

Similarly, except for recitation of a single chain antibody against NF-AT3 (p.28, last paragraph bridging p.29), and two calcineurin inhibitors, cyclosporin A, and FK506 (Example 5 on page 76), which are known in the art, and which however are not disclosed as binding to NF-AT3, the structure of numerous other competitive inhibitors of NF-AT3 (p.30, line 21), as well as numerous peptides that **bind** to and inactivate NF-AT3 is not disclosed in the specification.

The recitation of a single chain antibody against NF-AT3 (p.28, last paragraph bridging p.29), and two calcineurin inhibitors, cyclosporin A, and FK506, which are not disclosed as binding to NF-AT3, would not be a representative number of small

molecule inhibitors that **bind to** and inactivate of NF-AT3, such as GATA4 and NF-AT3 mimetics, small antisense molecules that inhibit **in vivo** function of NF-AT3, numerous other competitive inhibitors of NF-AT3, such as numerous other peptides and non-peptide molecules that inhibit NF-AT3, the structure of none of which is disclosed, nor known in the art.

There is no suggestion in the specification of how such compound could be made or otherwise obtained other than by trial-and-error. No three dimensional structure of GATA4 or NF-AT3 is disclosed in the specification, nor in the art.

It is noted that in a recent 2004 court case (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) the court states that "even with the three dimensional of enzymes such as COX-1 and COX-2 in hand, it may even now not be within the ordinary skill in the art to predict what compounds might bind to and inhibit them". The present application is similar to that in Rochester case, in that although the structure of GATA4 or NF-AT3 is known in the art, and except for antibody inhibitor of NF-AT3, one cannot predict what other mimetics or antisense compounds might bind to and inactivate NF-AT3, especially in view that three dimensional structure of GATA4 or NF-AT3 is not even disclosed in the specification or known in the art.

Similarly, although small antisense molecules that inhibit NF-AT3 in vitro could be routinely screened in vitro, which small antisense molecules that inhibit NF-AT3 in vivo could not be predicted, in view of the unpredictability of antisense treatment in vivo, as taught by Gura et al, of record.

Moreover, no common structure of the claimed small molecules that bind to and inactivate NF-AT3, which range from single chain antibodies to numerous mimetic peptides other than antibodies, to antisense oligonucleotides, and other non-peptide organic and inorganic molecules that bind to and inactivate NF-AT3, is disclosed in the specification, nor is it known in the art.

The court stated that:

> a generic statement such as "vertebrate insulin cDNA or mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406.

Thus the instant application does not meet the requirement of Lilly, which is applicable to the instant application, because the recitation of a single chain antibody against NF-AT3 (p.28, last paragraph bridging p.29), and two calcineurin inhibitors, cyclosporin A, and FK506, which however are not disclosed as binding to NF-AT3, would not constitute an adequate representative number of species of small molecule

mimetics, small antisense molecules that inhibit **in vivo** function of NF-AT3, numerous other competitive inhibitors of NF-AT3, such as numerous other peptides and non-peptide molecules that inhibit NF-AT3, in view that the structure of the claimed GATA4 mimetics, antisense molecules that inhibit **in vivo** function of NF-AT3, and numerous peptide and non-peptide competitive inhibitors of NF-AT3 is not disclosed in the specification, and further in view that there is no disclosure of common structural attributes among the claimed genus of small molecule inhibitors.

Further, the instant specification does not meet the written description requirement per Enzo, because the specification does not show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

Thus, the specification does not provide an adequate written description of small molecule inhibitors of NF-AT3 that is required to practice the claimed invention. Since the specification fails to adequately describe the product for use in the claimed method, it also fails to adequately describe the claimed method of treating hypertrophy.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Claims 1, 4, 9 are rejected under 35 USC 112, first paragraph, because the specification, while being enabling for a method for treating hypertrophy in a cardiomyocyte cell, comprising contacting NF-AT3 with an agent that binds to and

inactivates NF-AT3, wherein said agent is an antibody, does not reasonably provide enablement for a method for treating hypertrophy in a cardiomyocyte cell, comprising contacting NF-AT3 with an agent that binds to and inactivates NF-AT3, wherein said agent is "a small molecule inhibitor" for reasons of record in paper of 03/18/04.

Applicant argues that it is not clear what is not enabled. Applicant argues that the use of mimetics and antisense are not called out by the claims at issues.

This is not found to be persuasive. It is clear from previous Office action that the claims are not enabled for a method for treating hypertrophy using the genus "small molecule inhibitors" that bind to and inactivate NF-AT3. Although the claims do not specifically recite mimetics and antisenses for use in the claimed method, the language "small molecule inhibitors" encompass peptides mimetics, non-peptide organic or inorganic mimetics and antisenses that bind to and inactivate NF-AT3. Thus it is clear that the current rejections apply to the current claims.

Applicant argues that the Examiner's criticism seems to rise to the level of working model, a criticism the Examiner has failed to address. Applicant argues that a single example of in vivo proof that the use of NF-AT3 inhibitors can be a method for treating hypertrophy is adequate (Example 6 and 9). Applicant argues that the specification describes the mimetic technology, and thus it is not required to make something that is readily understood by one of skill in the art.

This is not found to be persuasive. Although Applicant discloses in Example 5 that cyclosporin A and FK506 inhibit the hypertrophic effect of AngII or PE, it is noted that cyclosporin A and FK506 acts by inhibiting calcineurin, and there is no disclosure in

the specification that cyclosporin A and FK506 bind to and inactivate NF-AT3, and thus cyclosporin A and FK506 would not be representative of the broadly claimed small molecule inhibitors that bind to and inactivate NF-AT3 for use in the claimed method. Further, the recited single chain antibody against NF-AT3 would not have any structural relationship with the broadly claimed small molecule inhibitors that bind to and inactivate NF-AT3, such as peptides mimetics, non-peptide organic or inorganic mimetics and antisenses that bind to and inactivate NF-AT3, the structure of none of which is disclosed in the specification.

Further, although the mimetic technology is known in the art, obtaining successful mimetics of GATA4 or NF-AT3 that bind to and inactivate NF-AT3 would be only by trial-and-error, especially no three dimensional structure of GATA4 or NF-AT3 is disclosed in the specification, nor in the art. It is noted that in a recent 2004 court case, *Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004, the court states that "even with the three dimensional of enzymes such as COX-1 and COX-2 in hand, it may even now not be within the ordinary skill in the art to predict what compounds might bind to and inhibit them".

In view of the above, one would not know how to make the broadly claimed small molecule inhibitors that bind to and inactivate NF-AT3 for use in the claimed method of treating hypertrophy.

Concerning Applicant's comment that the Examiner requires a working example, although a working example is not always required, it is noted however that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the

invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the unpredictability of the structure of the broadly claimed small molecule inhibitors that bind to and inactivate NF-AT3 for use in the claimed method of treating hypertrophy, the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Applicant argues that the Examiner is convinced that the language "potentially " in the statement by Bennett, 1998, that it is possible to utilize antisense oligonucleotides as effective research tools and "potentially" as therapeutic agent, supports the Examiner case that antisense is non-enabled technology, and ignores the explicit teaching of the reference that antisense is a viable and utilizable technology.

This is not found to be persuasive. It is noted that Applicant distorts the Examiner position. The Examiner did not recite that the antisense technology is not enabled, but

rather the antisense technology is an unpredictable field, despite there is successful use of antisense in some circumstances, in view of the teaching of Gura et al.

Thus since the claims encompass use of antisense in gene therapy for treating hypertrophy, and since antisense technology is unpredictable as taught by Gura et al, of record, and further since gene therapy is also unpredictable, as taught by Miller et al,1995, Deonarian et al, 1998, a similar date as the date of Applicant's recited Bennett et al, 1998, Verma et al, 1997, and Crystal et al, 1995, all of record, it would be undue experimentation for one of skill in the art to practice the claimed method.

REJECTION UNDER 35 USC 102(b)

Claim 1 remains rejected under 35 USC 102(b) as being anticipated by Haverich et al, or Ried et al, as evidenced by McCaffrey et al, and Martinez-Martinez et al, for reasons already of record in paper No.26.

Applicant argues as follows:

Applicants assert that every element in claim 1 is not found in any of the prior art references. Applicant argues that the Examiner misreads the claims at issue, as the Examiner asserts that the method is to treatment of cardiomyocyte, when clearly claim 1 is directed to a method for treating cardiac hypertrophy.

Applicant asserts that Claim 1 teaches treatment of hypertrophy by inhibiting the function of NT-AT3 in a cardiomocyte using a compound that inhibits the function of NF-AT3. Applicant asserts that the Haverich and Reid references teach the use of cyclosporin A (CsA) for treatment of transplantation disease; they do not teach, much

less suggest treatment of hypertrophy or effects on cardiac structure. They are instead directed towards improving cardiac function in a post-transplant environment. Additionally, while the Mccaffrey and Martinez-Martinez references do teach that CsA is an NF-AT3 inhibitor, they do not teach the use of an NF-AT3 inhibiting compound to treat hypertrophy. Not one of these references teaches the invention, nor do the collection of them inherently predict or assert the invention.

Applicant asserts that Novitski merely states that inherent anticipation may lie, that claims are interpreted as broadly as reasonably possible, and that limitations are not read into the claims. Applicant asserts that however, a limitation of the instant claims is treating cardiac hypertrophy. Thus, nothing must be read into the claims, and the claims cannot be read to exclude this limitation.

As pointed out before, applicant submits that the case law requires that an inherent disclosure "must be certain". Ex parte Mcoueen, 123 USPQ 37 (Bd. App. 1958). There is no evidence from the cited references that hypertrophy had been treated or even analyzed. The prior art specifically deals with transplantation disease and cardiac function after transplant in response to CsA application.

Applicant argues that transplantation disease has not and is not defined as cardiac hypertrophy, and it is possible to have one without the other, thus, there cannot be any inherency. The references do not teach a treatment for hypertrophy nor would one of skill in the art be expected to infer from these references that CsA, and subsequently NF-AT3 inhibitors, were being used to treat hypertrophy. Applicant asserts

that the examiner has not even attempted to address this issue, instead merely repeating the previous rejection.

Applicant's arguments set forth in paper of 08/17/04 have been considered but are not deemed to be persuasive for the following reasons:

Applicant distorts the Examiner position when arguing that the Examiner asserts that the method is to treatment of cardiomyocyte, when clearly claim 1 is directed to a method for treating cardiac hypertrophy.

The Examiner did not assert that the claimed method is to treatment of cardiomyocyte. Rather, the Examiner position has been and is that although the art does not recite that the cited method would be effective in treating hypertrophy, however, since the art method steps are the same as the claimed method steps, i.e., inhibiting the function of NF-AT3, using the same claimed composition, i.e., in a cardiomyocyte, one would expect that inherently the method taught by the art would have the same effect as the claimed method. There is no limitation of hypertrophic cardiomyocyte as a composition for use in the method of claim 1.

It is noted that Novitski teaches that "Because the method of the prior art comprises the same method steps as claimed in the instant invention using the same composition, the claimed method is anticipated because the method will inherently lead to the claimed effects". See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

January 13, 2005